

# **EXHIBIT A**



DEPARTMENT OF HEALTH & HUMAN SERVICES

SEP 10 2013

Food and Drug Administration  
10903 New Hampshire Avenue  
Building #51  
Silver Spring, MD 20993

Andrew Kolodny, MD  
President, Physicians for Responsible Opioid Prescribing  
920 48<sup>th</sup> Street, Suite 1510  
Brooklyn, NY 11219

Re: Docket No. FDA-2012-P-0818

Dear Dr. Kolodny:

This letter responds to the citizen petition submitted by Physicians for Responsible Opioid Prescribing (PROP), which was received by FDA on July 26, 2012 (Petition). The Petition describes PROP's concerns about the safety and efficacy of opioid analgesic drugs for long-term use in chronic non-cancer pain, and requests that the Food and Drug Administration (FDA or Agency): (1) “[s]trike the term ‘moderate’ from the indication [of opioid analgesics] for non-cancer pain”; (2) “[a]dd a maximum daily dose, equivalent to 100 milligrams of morphine for non-cancer pain”; and (3) “[a]dd a maximum duration of 90-days for continuous [daily] use” for non-cancer pain (Petition at 2).<sup>1</sup>

FDA has carefully reviewed PROP's Petition and the numerous comments submitted to the public dockets<sup>2</sup> by government entities, medical societies, healthcare providers, patients, and other members of the public. For the reasons described in detail in this response, the Petition is granted in part and denied in part.

Today, on the basis of the information discussed below, FDA has notified application holders for extended-release/long-acting (ER/LA) opioid analgesics that, pursuant to section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C 355(o)(4)), important safety labeling changes are needed to the labeling of ER/LA opioid analgesics.<sup>3</sup> It is the agency's intent that these changes, which are described more fully below, will help more effectively communicate the serious risks of misuse, abuse, neonatal opioid withdrawal syndrome (NOWS), addiction, overdose, and death associated with the use of ER/LA opioids overall, and during pregnancy. FDA has also determined that more data are needed about the safety of long-term use of opioids. Pursuant to section 505(o)(3) of the FD&C Act, FDA is therefore requiring all new drug application (NDA) sponsors of ER/LA opioids to conduct postapproval studies and clinical trials

<sup>1</sup> The Petition requests pertain to analgesia products; therefore, this response is limited to opioids with indications for analgesia.

<sup>2</sup> FDA received comments on the PROP citizen petition in the above-captioned docket and comments relevant to the PROP citizen petition in the docket for a part 15 hearing the agency held in February 2013, titled Impact of Approved Drug Labeling on Chronic Opioid Therapy (Part 15 Hearing) (see Docket No. FDA-2012-N-1172).

<sup>3</sup> Pursuant to section 505(o)(4) of the FD&C Act, FDA is notifying holders of approved NDAs and holders of approved ANDAs that reference a NDA that is not currently marketed.

(post-marketing requirements, or PMRs) to assess certain known serious risks of ER/LA opioid use: misuse, abuse, hyperalgesia, addiction, overdose, and death.

## I. BACKGROUND

### A. Opioids

Opioids are a class of powerful pain-relieving agents that includes oxycodone, hydrocodone, and morphine, among others. When prescribed and used properly, opioids can effectively manage pain and alleviate suffering—clearly a public health priority.<sup>4</sup> Chronic pain is a serious and growing public health problem: it “affects millions of Americans; contributes greatly to national rates of morbidity, mortality, and disability; and is rising in prevalence.”<sup>5</sup> There is also evidence that pain is inadequately treated in many patients.<sup>6</sup> However, pain is a self-reported symptom that is difficult to quantify, and its treatment is complex.

Opioids also have grave risks, the most well-known of which include addiction, overdose, and even death. The labeling for these products contains prominent warnings about these risks. Moreover, the boxed warning states that all patients should be “routinely monitor[ed]...for signs of misuse, abuse, and addiction.” Even proper use of opioids under medical supervision can result in life-threatening respiratory depression, coma, and death (see Boxed Warning and Section 5.3 of Warnings in current labeling). Indeed, a Centers for Disease Control and Prevention (CDC) analysis published in February 2013 documents an 11th straight year of increases in drug overdose deaths, with opioids being involved in 75% of pharmaceutical overdose deaths, either alone or in combination with other drugs.<sup>7</sup>

Most opioid-only drugs are controlled under Schedule II of the Controlled Substances Act.<sup>8</sup> By law, prescriptions for Schedule II drugs cannot be refilled; patients need a new prescription to obtain the drug beyond the initial number of doses prescribed.<sup>9</sup> There are also strict recordkeeping, reporting, and physical security requirements. This level of

---

<sup>4</sup> See “Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research.” Committee on Advancing Pain Research, Care, and Education; Institute of Medicine. 2011:1-364 (available at [http://www.nap.edu/catalog.php?record\\_id=13172](http://www.nap.edu/catalog.php?record_id=13172)).

<sup>5</sup> *Id.* at p. 5.

<sup>6</sup> *Id.* at p. 1.

<sup>7</sup> Jones CM, Mack, KA, Paulozzi LJ. Pharmaceutical overdose deaths, United States, 2010. JAMA 2013; 309(7): 657-9.

<sup>8</sup> See 21 U.S.C. 801 *et seq*; 21 CFR 1308.12. There are some opioids in Schedule III (e.g., buprenorphine, see 21 CFR 1308.13(e)(2)(i)) and Schedule IV (e.g., butorphanol and pentazocine, see 21 CFR 1308.14(f)). Tramadol, a synthetic opioid, is not currently scheduled under the Controlled Substances Act, see [www.deadiversion.usdoj.gov/drug\\_chem\\_info/tramadol.pdf](http://www.deadiversion.usdoj.gov/drug_chem_info/tramadol.pdf).

<sup>9</sup> Although opioid drug labeling does not recommend a limit on the number of doses a patient should receive, the Schedule II status of most opioid drugs imposes certain restrictions on their availability. 21 CFR 1306.12(a). However, prescribers “may issue multiple prescriptions authorizing the patient to receive a total of up to a 90-day supply of a Schedule II controlled substance” as long as certain conditions are met. 21 CFR 1306.12(b)(1).

control reflects a finding that most opioid drugs have “high potential for abuse” and that “[a]buse of the drug . . . may lead to severe psychological or physical dependence.”<sup>10</sup>

Opioid drugs have been approved for different conditions of use based on the data and information submitted by the sponsor of each drug product. Accordingly, product labeling may vary among approved opioid drugs, and such drugs may be prescribed to different patient populations.<sup>11</sup> The approved indications for ER/LA opioid analgesics are uniform, however. These drugs are currently indicated “for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.”<sup>12</sup> The current labeling for these drugs also contains a prominent statement that they are not for use:

- As an as-needed (prn) analgesic,
- For pain that is mild or not expected to persist for an extended period of time,
- For acute pain,
- In the immediate postoperative period, or
- For postoperative pain, unless the patient is already receiving chronic opioid therapy prior to surgery, or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time.<sup>13</sup>

The labeling for some ER/LA opioid analgesics also states that they are for use (or for use at higher doses) only in opioid-tolerant patients.<sup>14</sup>

---

<sup>10</sup> 21 U.S.C. 812(b)(2).

<sup>11</sup> For example, indications for which particular IR opioid products have been approved include “the management of acute and chronic moderate to severe pain where the use of an opioid analgesic is appropriate” (Oxecta (oxycodone hydrochloride) labeling, available at [www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/202080s001lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/202080s001lbl.pdf)); “the relief of mild to moderately severe pain where the use of an opioid analgesic is appropriate” (Codeine sulfate (NDA 022402) labeling, available at [www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/022402s006lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022402s006lbl.pdf)); and “the management of pain in patients where an opioid analgesic is appropriate” (Dilaudid (hydromorphone hydrochloride) labeling, available at [www.accessdata.fda.gov/drugsatfda\\_docs/label/2007/019892s015lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/019892s015lbl.pdf)).

<sup>12</sup> OxyContin (oxycodone hydrochloride) extended-release tablets (NDA 022272) labeling, available at [www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/022272Orig1s014lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022272Orig1s014lbl.pdf).

<sup>13</sup> Labeling for OxyContin (oxycodone hydrochloride) extended-release tablets (NDA 022272), available at [www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/022272Orig1s014lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022272Orig1s014lbl.pdf) (internal references omitted).

<sup>14</sup> See, e.g., labeling for Exalgo (hydromorphone hydrochloride) (NDA 021217) and Duragesic (fentanyl) (NDA 019813). Further, certain opioid drugs also have limitations of use on the higher doses, with labeling stating that higher doses are for opioid-tolerant patients only. See, e.g., labeling for Avinza (morphine sulfate) extended-release capsules (NDA 021260), available at [www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/021260s017lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021260s017lbl.pdf) and OxyContin (oxycodone hydrochloride) extended-release tablets (NDA 022272), available at [www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/022272Orig1s014lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022272Orig1s014lbl.pdf).

## B. ER/LA Opioid Analgesic Risk Evaluation and Mitigation Strategy

FDA approved a shared-system Risk Evaluation and Mitigation Strategy (REMS) for ER/LA opioid analgesics on July 9, 2012 (ER/LA Opioid Analgesic REMS).<sup>15</sup> The goal of the ER/LA Opioid Analgesic REMS is to “reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of [ER/LA opioids] while maintaining patient access to pain medications.”<sup>16</sup> Under the REMS, “[a]dverse outcomes of concern include addiction, unintentional overdose, and death.”<sup>17</sup> The REMS is currently limited to ER/LA opioid products because FDA has concluded that there are disproportionate safety concerns associated with these products compared to immediate-release (IR) opioids.<sup>18</sup>

Currently, more than 30 products are subject to the ER/LA Opioid Analgesic REMS.<sup>19</sup> The ER/LA Opioid Analgesic REMS contains requirements for distribution of a Medication Guide with each prescription filled, as well as a requirement that training be made available to all those who prescribe ER/LA opioids. Prescriber education training is considered ER/LA Opioid Analgesic REMS-compliant if, among other things, it includes the elements described in the “FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics” (FDA Blueprint).<sup>20</sup> The FDA Blueprint provides guidance to prescribers to enable appropriate ER/LA opioid prescribing practices, as well as information prescribers can use in counseling patients about the risks and benefits of ER/LA opioid use.

## C. Public Input

FDA has received a considerable amount of input from stakeholders and other commenters on issues pertaining to the benefits and risks of opioid use. For example, FDA participated in a two-day workshop in May 2012 hosted at the National Institutes of Health (NIH), called, “Assessment of Analgesic Treatment of Chronic Pain: A Scientific Workshop.”<sup>21</sup> Several stakeholders and other members of the public gave presentations

---

<sup>15</sup> See

[www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf](http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf) (most recently modified in April, 2013).

<sup>16</sup> *Id.* at p. 2.

<sup>17</sup> *Id.*

<sup>18</sup> See <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm309742.htm#Q5>; see also, e.g., Dormitzer, C. Opioid Abuse and Misuse: Data from the National Survey on Drug Use and Health and the Drug Abuse Warning Network. Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM). UMUC Inn and Conference Center by Marriott, Adelphi, MD, July 22-23, 2010 (available at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM220950.pdf>) (providing data showing growing harm associated with ER/LA opioids).

<sup>19</sup> The list of drugs required to have a REMS, grouped by application holder, may be found at [www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM348818.pdf](http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM348818.pdf).

<sup>20</sup> Available at <http://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf>.

<sup>21</sup> See Docket No. FDA-2012-N-0067; see also <http://www.fda.gov/Drugs/NewsEvents/ucm283979.htm>.

about issues relating to opioid treatment of chronic pain, and additional comments and subsequent input were posted to the public docket for that meeting.<sup>22</sup>

On February 7 and 8, 2013, FDA held a public hearing on chronic use of opioid drug products, titled, “Impact of Approved Drug Labeling on Chronic Opioid Therapy” (Part 15 Hearing).<sup>23</sup> FDA requested information, particularly scientific evidence, on issues pertaining to the use of opioid drugs in the treatment of chronic pain, including diagnosis and understanding of pain, understanding and adhering to the labeling of pain-treating products, and limiting opioid prescriptions and use.<sup>24</sup> The Agency received input from dozens of presenters, including patients, individuals who had lost loved ones due to opioids, clinicians, public health experts, professional associations, academicians, and others, including PROP. FDA also received over 600 comments to the Part 15 Hearing docket. The majority were from patients voicing concerns that labeling changes could make legitimate patient access to opioid analgesics more difficult.<sup>25</sup> The remainder reflected the same diversity of viewpoints and concerns presented during the hearing itself.

FDA also received more than 1900 comments on the PROP Petition. Many public health agencies and organizations supported the requests in the Petition, citing concerns about increased opioid use and abuse.<sup>26</sup> However, the majority of comments opposed PROP’s requests. Many professional societies (*e.g.*, the American Academy of Pain Medicine, the American Medical Association, the American Society of Anesthesiologists, the American Pain Society) did not support the Petition and stated that the data cited by PROP did not support PROP’s requests (particularly those requests for limits on dose and duration of use of opioids). Professional societies also expressed concern that the labeling changes requested by PROP were not supported by scientific evidence, and that a “one-size-fits-all” approach to a maximum dose or duration of treatment would be problematic and inconsistent with the need for individualized treatment and the variability among patient responses to opioids.<sup>27</sup>

---

<sup>22</sup> See Docket No. FDA-2012-N-0067.

<sup>23</sup> See Docket No. FDA-2012-N-1172.

<sup>24</sup> See [www.gpo.gov/fdsys/pkg/FR-2012-12-19/pdf/2012-30516.pdf](http://www.gpo.gov/fdsys/pkg/FR-2012-12-19/pdf/2012-30516.pdf).

<sup>25</sup> However, for privacy reasons, many comments from individual patients are not publicly available on [www.regulations.gov](http://www.regulations.gov). They nevertheless are considered to be included in the public docket.

<sup>26</sup> See, *e.g.*, comments from the New York City Department of Health and Mental Hygiene (Docket No. FDA-2012-P-0818-0785); County of Los Angeles Public Health (Docket No. FDA-2012-P-0818-0336); Denver Public Health (Docket No. FDA-2012-P-0818-0677); and the National Center on Addiction and Substance Abuse at Columbia University (Docket No. FDA-2012-P-0818-0691).

<sup>27</sup> See, *e.g.*, comments from the American Academy of Pain Medicine (Docket No. FDA-2012-P-0818-0165); the American Medical Association (Docket No. FDA-2012-P-0818-0783); the American Society of Anesthesiologists (Docket No. FDA-2012-P-0818-0246); the American Pain Society (Docket No. FDA-2012-P-0818-0187); the American Academy of Physical Medicine and Rehabilitation (Docket No. FDA-2012-P-0818-0658); the American Society of Regional Analgesia and Pain Medicine (Docket No. FDA-2012-P-0818-0276); the Texas Pain Society (Docket No. FDA-2012-P-0818-0331); and the Florida Academy of Pain Medicine (Docket No. FDA-2012-P-0818-0333). Some commenters submitted critiques of PROP’s cited studies that identified the studies’ limitations. See, *e.g.*, comments from the American Academy of Pain Medicine (Docket No. FDA-2012-P-0818-0165). For example, the Florida Academy of Pain Medicine states, “it appears that the petitioners are asking for changes to the indications for long-term

## II. SAFETY LABELING CHANGES

After evaluating stakeholder and commenter input regarding opioid labeling, and based on FDA's review of relevant literature, FDA has determined that safety labeling changes to the labeling of ER/LA opioid analgesics are needed to more effectively communicate to prescribers the serious risks associated with these drugs, and to more clearly describe the population in whom these drugs should be used in light of these serious risks—thus encouraging better prescribing, monitoring, and patient counseling practices involving these drugs. FDA is therefore exercising its authority under section 505(o)(4) of the FD&C Act to notify application holders that modifications to ER/LA opioid analgesic labeling are needed.<sup>28</sup> It is the agency's intent that these changes will help reduce inappropriate prescribing<sup>29</sup> and help curb the increase in misuse, abuse, NOWS, addiction, overdose, and death associated with ER/LA opioid analgesic use.

These safety labeling changes apply only to ER/LA opioid analgesics, and, at present, FDA is not requesting or requiring that any labeling changes be made to IR opioids or opioid/non-opioid combination products (which include both an IR opioid and a non-opioid analgesic).<sup>30</sup> Much of the literature FDA reviewed assessed opioid use from all opioid sources, or did not necessarily separate data according to opioid formulation (*i.e.*, ER/LA versus IR or opioid/non-opioid combinations). However, FDA recognizes that ER/LA opioids, as a class of drugs, have disproportionate safety concerns compared to IR opioids or opioid/non-opioid combination products; indeed, the recognition of

---

high-dose opioid therapy (LTHDOT) for non-cancer pain, based on a small number of studies with significant methodological shortcomings and findings that are not conclusive. In short, they are basing their request for label changes on the same kind of evidence they themselves, criticize as being insufficient to support the safety and efficacy of LTHDOT for non-cancer pain" (Docket No. FDA-2012-P-0818-0333).

<sup>28</sup> Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amended the FD&C Act, as codified in section 505(o)(4) of the FD&C Act, to authorize FDA to require holders of approved drug applications to make safety labeling changes (SLCs) if the agency becomes aware of "new safety information" that FDA determines should be included in the labeling of the drug. *New safety information* is information derived from a clinical trial, an adverse event report, a post-approval study (including a study under section 505(o)(3) of the FD&C Act), or peer-reviewed biomedical literature; data derived from the post-market risk identification and analysis system under section 505(k) of the FD&C Act; or other scientific data deemed appropriate by the Agency about, among other things, a serious or an unexpected serious risk associated with use of the drug of which the Agency has become aware (that may be based on a new analysis of existing information) since the drug was approved, the REMS was approved, or since the last assessment of the approved REMS; or the effectiveness of the approved REMS for the drug obtained since the last assessment of such strategy. See section 505-1(b)(3) of the FD&C Act.

<sup>29</sup> Pain patients in the United States receive care from prescribers with different backgrounds and levels of experience and expertise in treating pain. IMS Health, Vector One®: National (VONA). Data Extracted September 2012. Weblink:

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM337148.pdf>. For example, some prescribers may not understand how to identify patients at risk for addiction, how to identify behaviors associated with misuse and abuse, and how to manage patients who are receiving opioids for chronic pain so as to reduce the risks of misuse, abuse, NOWS, addiction, overdose and death.

<sup>30</sup> Therefore, the agency denies PROP's Petition insofar as it requests labeling changes for IR opioids, or opioid/non-opioid combination products.

disproportionate safety concerns for ER/LA opioids informed FDA's decision to require the ER/LA Opioid Analgesic REMS. For example, data show that the risk for misuse and abuse is greater for ER/LA opioids.<sup>31</sup> Because they are intended to release the drug over a longer period of time, many ER/LA opioids contain higher doses of opioids compared to IR opioids or opioid/non-opioid combinations. This increases the risk of a fatal outcome in the event of an overdose, and may make ER/LA opioids more desirable in the eyes of opioid abusers and addicts. Furthermore, ER/LA opioids are often used in a chronic pain setting. Thus, in light of the risks posed by ER/LA opioids, and the totality of available data on both ER/LA opioids specifically and opioid drugs in general, the Agency has decided to make ER/LA opioid analgesics its current focus.

First, FDA is requiring changes to the boxed warning for ER/LA opioid analgesics to give greater emphasis and prominence to the risks of misuse, abuse, NOWS, addiction, overdose, and death. For example, the first sentence of the new boxed warning provides that ER/LA opioids "expose patients and other users to the risks of opioid addiction, abuse, and misuse which can lead to overdose and death." The new boxed warning also urges prescribers to "assess each patient's risk" before prescribing, and to "monitor all patients regularly for the development of these behaviors or conditions."

Second, FDA is requiring changes to the Indications and Usage section of the labeling. As noted above, ER/LA opioid analgesics currently are "indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time."<sup>32</sup> The Agency has concluded that use of terminology predicated only on a categorical "severity scale" (e.g., mild, moderate, severe) to characterize the intensity of pain for which ER/LA opioids are indicated does not sufficiently focus prescribers' attention on their responsibility to make an individualized assessment of patient needs in light of the serious risks of ER/LA opioids. Given these serious risks, especially those of overdose and death, the Agency believes that clarity as to the appropriate use of such drugs is of the utmost importance. The new language clearly communicates to prescribers that ER/LA opioid analgesics should be used only when alternative treatments are inadequate because of the serious risks of these drugs. The new language also identifies specific examples of alternative treatment options, namely, "non-opioid analgesics or immediate-release opioids," and provides additional guidance on when such treatments may be deemed inadequate to provide sufficient management of pain.

Furthermore, the new labeling language underscores that patients in pain should be assessed not only by their rating on a categorical pain intensity scale, but also based on a

---

<sup>31</sup> Dormitzer, C. Opioid Abuse and Misuse: Data from the National Survey on Drug Use and Health and the Drug Abuse Warning Network. Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM). UMUC Inn and Conference Center by Marriott, Adelphi, MD, July 22-23, 2010 (available at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM220950.pdf>).

<sup>32</sup> See, e.g., OxyContin (oxycodone hydrochloride) extended-release tablets (NDA 022272) labeling, available at [www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/022272Orig1s014lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022272Orig1s014lbl.pdf).

more thoughtful determination that their pain — however it may be defined — is *severe enough* to require daily, around-the-clock, long-term opioid treatment, *and* for which alternative treatment options are inadequate. This framework better enables prescribers to make decisions based on a patient's individual needs, given the serious risks associated with ER/LA opioids, against a backdrop of alternatives such as IR opioids and non-opioid analgesics. It allows prescribers to make an assessment of pain relative to a patient's ability to perform daily activities or enjoy a reasonable quality of life, not only on where a patient's pain falls on an intensity scale, and assess if ER/LA opioids are needed after determining whether (a) the pain is severe enough to require daily, around-the-clock, long-term opioid treatment, and (b) if alternatives to ER/LA opioids are inadequate to manage such pain, in light of the serious risks associated with ER/LA opioid analgesics.

The revised indication language reads as follows:

**"[Tradename] is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate."**

**Limitations of Use**

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve [Tradename] for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
- [Tradename] is not indicated as an as-needed (prn) analgesic."

This new language is intended to prompt prescribers to more closely assess each individual patient's condition, and carefully evaluate whether alternative treatment options such as non-opioid analgesics or IR opioids are appropriate. The new language is intended to reflect that ER/LA opioid analgesics should be prescribed only when the prescriber determines that such alternatives are ineffective, not tolerated, or would otherwise be inadequate.

Third, FDA is notifying application holders of the need for changes to the Dosage and Administration, Warnings and Precautions, Drug Interactions, and Use in Specific Populations sections of ER/LA opioid analgesic labeling. These changes are specifically intended to urge prescribers to weigh carefully whether the benefits of an ER/LA opioid outweigh its serious risks on a patient-by-patient basis. If an ER/LA opioid analgesic is prescribed, the labeling changes emphasize that prescribers should monitor patients carefully for signs of abuse and addiction. FDA is also notifying application holders of the need for changes to the Patient Counseling Information and the product-specific Medication Guides to improve the communication of risks to patients.<sup>33</sup> The Agency

---

<sup>33</sup> Following the approval of the safety labeling changes, a REMS modification will be required to incorporate the approved safety labeling changes into the REMS materials, as applicable.

believes that the changes will improve communication of serious risks associated with the use of these products and help improve the safe use of ER/LA opioid analgesics overall.

FDA intends these changes to enable not only a more careful and thorough approach to determining whether ER/LA opioid analgesics should be prescribed for a particular patient, but also allows prescribers to better assess whether the serious risks associated with ER/LA opioids, including the risks of misuse, abuse, addiction, overdose and death associated with ER/LA formulations, are offset by the benefits ER/LA opioids may provide in managing pain for an individual patient.

Accordingly, PROP's request that FDA remove the term "moderate" from the indication for ER/LA opioid analgesic drugs is granted for the reasons explained above. As explained above, the changes to the labeling also reflect a departure from an indication based solely on a severity scale, and transitions to an indication that facilitates careful prescribing decisions based on an individualized assessment of a patient's situation (*i.e.*, whether an individual's pain is severe enough to require daily, around-the-clock, long-term opioid treatment) and a heightened recognition that, because of the serious risks associated with the use of these drugs, ER/LA opioids should be used only when alternative treatment options are inadequate.<sup>34</sup>

All of PROP's labeling change requests are limited to "non-cancer" pain, a distinction that is not made in current ER/LA opioid analgesic labeling. It is FDA's view that a patient without cancer, like a patient with cancer, may suffer from chronic pain, and PROP has not provided scientific support for why labeling should recommend different treatment for such patients. In addition, FDA knows of no physiological or pharmacological basis upon which to differentiate the treatment of chronic pain in a cancer setting or patient from the treatment of chronic pain in the absence of cancer, and comments to the Petition docket reflect similar concerns.<sup>35</sup> FDA therefore declines to make a distinction between cancer and non-cancer chronic pain in opioid labeling.<sup>36</sup>

In accordance with section 505(o)(4) of the FD&C Act, the ER/LA opioid analgesic application holders are required to submit by October 10, 2013, a supplement proposing changes to the approved labeling to reflect the new safety information, or else notify the Agency that they do not believe labeling changes are warranted and submit a statement detailing the reasons why changes are not warranted.<sup>37</sup>

<sup>34</sup> When other analgesics are contraindicated or ineffective, restricting the indication of opioid drugs to treatment of severe pain only could leave some patients with chronic pain with an impaired ability to carry out daily activities, resulting in a diminished quality of life. See National Pharmaceutical Council (2001): Pain: Current Understanding of Assessment, Management, and Treatments, [http://www.npcnow.org/App\\_Themes/Public/pdf/Issues/pub\\_related\\_research/pub\\_quality\\_care/Pain-Current-Understanding-of-Assessment-Management-and-Treatments.pdf](http://www.npcnow.org/App_Themes/Public/pdf/Issues/pub_related_research/pub_quality_care/Pain-Current-Understanding-of-Assessment-Management-and-Treatments.pdf).

<sup>35</sup> See, e.g., comments from National Hospice and Palliative Care Organization (Docket No. FDA-2012-P-0678); Purdue Pharma (Docket No. FDA-2012-P-0818-0707).

<sup>36</sup> FDA notes that some epidemiology studies make distinctions between cancer and non cancer pain. However, while such classifications may be standard in epidemiological research, FDA believes that they are not relevant to ER/LA opioid labeling.

<sup>37</sup> See section 505(o)(4)(B) of the FD&C Act.

If the ER/LA opioid application holders do not submit the requested safety labeling changes, or if FDA disagrees with alternative language that the companies propose, the FD&C Act provides timelines under section 505(o)(4) for discussions regarding the labeling changes.<sup>38</sup> At the conclusion of these discussions, section 505(o)(4)(E) authorizes FDA to issue an order directing labeling changes as appropriate.

### III. POSTAPPROVAL SAFETY STUDIES AND CLINICAL TRIALS

ER/LA opioid drugs generally have been approved in part based on randomized, controlled clinical trials that lasted for a 12-week period. This is due, in part, to the fact that for chronic pain, it can be difficult to ensure subject participation in controlled trials beyond 12 weeks. Many commenters, including PROP, have voiced increasing concern about the lack of controlled clinical trial data evaluating opioid use longer than 12-weeks. FDA is not aware of adequate and well-controlled<sup>39</sup> studies of opioid use longer than 12 weeks.<sup>40</sup>

FDA has evaluated concerns pertaining to the serious risks of misuse, abuse, hyperalgesia,<sup>41</sup> addiction, overdose, and death associated with opioid use. The Agency acknowledges that the available data demonstrate an association—though not necessarily a causal relationship—between opioid dose and certain serious risks of opioid use. However, FDA also agrees that more data are needed regarding the relationship between opioid dose and adverse effects, and the relationship between opioid duration of use and adverse effects, before the Agency can determine whether additional action needs to be taken. More data are also needed on the point at which the risks of opioid use at escalating doses and longer durations of treatment may outweigh the benefits of opioid analgesic therapy.

Thus, FDA is exercising its authority under section 505(o)(3)(A) through (B) of the FD&C Act to require ER/LA opioid drug sponsors to conduct PMRs to assess the known serious risks of misuse, abuse, hyperalgesia, addiction, overdose, and death associated with the long-term use of opioid analgesics. FDA has established milestone dates for

---

<sup>38</sup> See section 505(o)(4)(D) of the FD&C Act.

<sup>39</sup> In this setting, “well-controlled studies” exclude active-controlled trials because they lack assay sensitivity, and failure to detect a statistically significant difference is difficult to interpret—either both drugs had the desired effect or both drugs did not have the desired effect.

<sup>40</sup> There are numerous uncontrolled studies that have evaluated patients on opioids for as long as a year; although some patients drop out of the studies over this period of time, many remain on opioid therapy, which may suggest that they continue to experience benefits that would warrant the risks of opioid use.

<sup>41</sup> Hyperalgesia is a known serious risk associated with chronic opioid analgesic therapy in which the patient becomes more sensitive to certain painful stimuli over time. See, e.g., Varney SM, Bebarta VS. Opioid-induced hyperalgesia--worsening pain in opioid-dependent patients . Am J Emerg Med. 2013 Feb;31(2):458.e5-6; Angst MS, Clark JD Opioid-induced Hyperalgesia A Qualitative Systematic Review. Anesthesiology 2006; 104:570–87. It also may lead to increased use of opioid analgesics. See, e.g., Chapman CR, Davis J, Donaldson GW, Naylor J, Winchester D. Postoperative pain trajectories in chronic pain patients undergoing surgery: the effects of chronic opioid pharmacotherapy on acute pain. J Pain 2011;12:1240-6.

completion of these studies and clinical trials, and is encouraging ER/LA opioid application holders to work together on these studies and clinical trials to provide the best information possible. First, the sponsors will have the opportunity to discuss with the Agency the particulars of the design and conduct of these PMRs.<sup>42</sup> We expect that this process will be completed in time for sponsors to submit final protocols to FDA within one year (*i.e.*, no later than August 2014). Sponsors must periodically report on the status of the studies and clinical trials.<sup>43</sup> The milestones for completion vary by study, with some expected to be completed as early as August 2015 and others expected to be completed in 2018.

As with the safety labeling changes, FDA is requiring PMRs only of ER/LA opioid analgesic application holders. While a majority of the literature that FDA reviewed did not distinguish between opioid formulation and/or composition, such as ER/LA versus IR opioids, or single ingredient opioids versus opioid/non-opioid combination products, FDA has made the determination that PMRs should be required of ER/LA opioid analgesic application holders to assess the known serious risks of misuse, abuse, hyperalgesia, addiction, overdose and death. FDA is taking this approach for the same reasons the Agency has decided to require safety labeling changes for ER/LA opioid analgesics: as discussed in greater detail in section II, above, FDA recognizes that ER/LA opioids, as a class of drugs, have disproportionate safety concerns compared to IR opioids or opioid/non-opioid combination products<sup>44</sup> and because ER/LA opioids are often used in a chronic pain setting. Thus, in light of the serious risks of ER/LA opioids, and the totality of available data, the Agency has decided to make ER/LA opioid analgesics its current focus for requiring PMRs.

#### **IV. REQUESTS FOR MAXIMUM DOSE AND DURATION OF USE**

The Agency declines to specify or recommend a maximum daily dose or duration of use for any opioid at this time, for the reason described below. However, FDA has determined that PMRs are necessary to assess the known, serious risks of misuse, abuse, hyperalgesia, addiction, overdose, and death. These studies will address, among other things, the effect of dose and duration of opioid use on these serious risks.

##### **A. Maximum Daily Dose**

PROP requests that FDA “add a maximum daily dose” of the equivalent of 100 milligrams (mg) of morphine (100 mg morphine equivalent dose (MED)) to opioids

---

<sup>42</sup> See Guidance for Industry, *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* (April 2011) at 12.

<sup>43</sup> Section 505(o)(3)(iii) of the FD&C Act.

<sup>44</sup> See, e.g., Dormitzer, C. Opioid Abuse and Misuse: Data from the National Survey on Drug Use and Health and the Drug Abuse Warning Network. Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM). UMUC Inn and Conference Center by Marriott, Adelphi, MD, July 22-23, 2010 (available at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM220950.pdf>).

(Petition at 2). In support of PROP's request, the Petition asserts that high-dose chronic opioid therapy is associated with increased risk of overdose death,<sup>45</sup> increased risk of emergency room visits,<sup>46</sup> and increased risk of fractures in the elderly.<sup>47</sup> (Petition at 2). PROP also maintains that "three large observational studies published in 2010 and 2011 found dose-related overdose risk" in patients on chronic opioid therapy (Petition at 2).

FDA agrees that adverse events and substance abuse of opioids occur at high doses—but adverse events can also occur at doses less than 100 mg MED. FDA also acknowledges that the available data do suggest a relationship between increasing opioid dose and risk of certain adverse events. However, the available information does not demonstrate that the relationship is necessarily a causal one. FDA has reviewed the studies cited in support of PROP's request, as well as studies cited in comments to the Petition docket and other studies described in the literature. For the reasons discussed in further detail below, the scientific literature does not support establishing a maximum recommended daily dose of 100 mg MED. Further, creating a maximum dose of 100 mg MED, or another dose ceiling, could imply a superior opioid safety profile under that set threshold, when there are no data to support such a conclusion. The Agency therefore denies PROP's request that opioid labeling specify a maximum daily dose.

*1. Cited Data Do Not Define a Relationship between Opioid Dose and Risk of Fractures in the Elderly*

FDA agrees that the Saunders study<sup>48</sup> PROP cites suggests a positive trend between opioid dose and fractures in the elderly. However, the elderly population is at risk for falls and fractures in general, and has more co-morbidities and more rapid fluctuations in health status than the overall adult population. The Saunders study did not take into account any co-morbidities in the elderly patients that arose after the initial patient visit when pain was diagnosed and an opioid was prescribed and the absence of that information may have confounded the results. Without additional data and a replication of the study's apparent finding, it would be premature to conclude that the risks of high-dose opioids outweigh their benefits in this population. Additionally, the highest dose-level in the Saunders study<sup>40</sup> was >50 mg MED, therefore, it did not directly address the 100 mg MED cutoff.

*2. Cited Data Do Not Define a Relationship between Opioid Dose and Emergency Room Visits*

---

<sup>45</sup> See Gomes T, Mamdani MM, Dhalla IA, et al., Opioid dose and drug-related mortality in patients with nonmalignant pain. Arch Intern Med, 2011; 171: 686-91.

<sup>46</sup> See Braden JB, Russo J, Fan MY, et al. Emergency department visits among recipients of chronic opioid therapy. Arch Intern Med 2010; 170:1425-32.

<sup>47</sup> See Saunders KW, Dunn KM, Merrill JO, et al., Relationship of opioid use and dosage levels to fractures in older chronic pain patients. J Gen Intern Med, 2010;25:310-5.

<sup>48</sup> Saunders KW, Dunn KM, Merrill JO, et al., Relationship of opioid use and dosage levels to fractures in older chronic pain patients. J Gen Intern Med, 2010;25:310-5.

FDA does not agree with PROP's contention that the Braden study<sup>49</sup> demonstrated a clear dose-response relationship between high dose opioid therapy and emergency room visits for recipients of chronic opioid therapy for non-cancer pain. Braden *et al.* examined the association between opioid dose and emergency room visits in two populations: a national, commercially insured population and a state-based publicly insured population. The study categorized opioid dose according to 3 levels: (1) 0 MED to the median MED of the population at issue<sup>50</sup> (Category 1); (2) the median MED of the given population to 120 mg MED/day (Category 2); and (3) >120 mg MED/day (Category 3). When compared to Category 1 patients, Category 2 and Category 3 patients appeared to have an increased risk of emergency room visits—but only in one study population. Furthermore, Category 3 patients did not appear to have a greater risk of emergency room visits than Category 2 patients in that study population. Taken together, the findings of this study were inconclusive with respect to the relationship between opioid dose and emergency room visits. Furthermore, FDA is concerned that this study did not fully adjust for important factors that may confound the association between opioid dose and health services use, such as race and income.<sup>51</sup> FDA therefore concludes that the Braden study does not support PROP's request to limit the maximum daily dose of opioids.

### *3. Cited Data Do Not Define a Relationship between Opioid Dose and Death*

PROP cites three observational studies (by Dunn, *et al.*,<sup>52</sup> Bohnert, *et al.*,<sup>53</sup> and Gomes, *et al*<sup>54</sup>) to support that higher doses of opioids are associated with higher risks of overdose-related death. Although these studies have several important limitations,<sup>55</sup> FDA agrees

<sup>49</sup> Braden JB, Russo J, Fan MY, *et al.*, Emergency department visits among recipients of chronic opioid therapy. *Arch Intern Med*, 2010; 170:1425-32.

<sup>50</sup> Note that the mean MED was different in the two study populations.

<sup>51</sup> Examples of other potential confounders include past health service use, alcohol use, or numbers of total medications used concurrently with opioids. See Braden JB, Russo J, Fan MY, *et al.*, Emergency department visits among recipients of chronic opioid therapy. *Arch Intern Med*, 2010; 170:1425-32.

<sup>52</sup> Dunn KM, Saunders KW, Rutter CM, *et al.*, Opioid prescriptions for chronic pain and overdose: a cohort study. *Annals of Internal Medicine*, 2010; 152:85-92.

<sup>53</sup> Bohnert AS, Valenstein M, Bair MJ, *et al.*, Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA*, 2011; 305:1315-21.

<sup>54</sup> Gomes T, Mamdani MM, Dhalla IA, *et al.*, Opioid dose and drug-related mortality in patients with nonmalignant pain. *Arch Intern Med*, 2011; 171: 686-91.

<sup>55</sup> For example, the Dunn and Gomes studies did not discuss the reason the patients had been prescribed opioid therapy. It is possible that the patients' underlying illnesses (or the severity thereof) may have increased the risk of death or other adverse events—and without additional information, FDA cannot evaluate PROP's assumption that these adverse events can be attributed to opioid use alone. None of the three studies—Dunn, Bohnert, or Gomes—examined the role of the opioid's formulation (e.g., IR vs. ER/LA opioids) in their analyses, and it is possible that different formulations may have differing impacts on overdose-related outcomes. In addition, none of the three studies included data about what doses the patients actually took (as opposed to the doses they were prescribed), or data about whether the patients complied with the instructions they received about proper opioid use. Indeed, in the Bohnert study, almost half of the decedent population experienced an unintentional opioid-related death when the maximum prescribed dose was equal to 0 mg per day—which raises questions not only about the amount of opioids

that these studies appear to credibly suggest a positive association between high-dose opioid use and the risk of overdose and/or overdose mortality. Indeed, these studies appear to demonstrate a statistically significantly higher risk of overdose death among those taking opioid doses of >100 mg MED compared to those taking opioid doses of 1-19 mg MED.

Unfortunately, the point at which the risk of overdose-related death increases enough to change the benefit-risk assessment of the studied opioids cannot be determined from these studies. Determining such a threshold would require a better understanding of how risk of overdose and/or overdose mortality changes along the continuum of opioid dose (from 0 mg through the highest doses taken by patients). This dose-response (*i.e.* overdose and/or overdose mortality) relationship should be analyzed treating opioid use as a continuous variable or using categories defined by small increments (*e.g.*, 1 mg MED, or per 5 mg MED). Thus, even though the aforementioned studies demonstrated a statistically significantly higher risk of overdose death for patients taking the highest studied doses compared with patients taking the lowest studied doses, the threshold for an increased risk associated with these drugs could actually be considerably lower or higher than a maximum daily dose of 100 mg MED.

## B. Maximum Duration of Treatment

The PROP Petition requests that FDA “[a]dd a maximum duration of 90 days for continuous (daily) use” (Petition at 2). In support of this request, the Petition alleges that “[l]ong-term safety and effectiveness of managing [pain] with opioids has not been established.” After a review of the literature cited in the Petition, and an assessment of other relevant information discussed below, FDA has determined that limiting the duration of use for opioid therapy to 90 days is not supportable. Thus, the Agency denies this request.

### I. Treatment Guidelines

In support of its request, PROP cites to the American Pain Society-American Academy of Pain Medicine Opioids Guidelines. However, these guidelines state that chronic opioid therapy can be an effective therapy for carefully selected and monitored patients.<sup>56</sup> The guidelines recommend individualized care, management plans, and monitoring—not a maximum duration of treatment.<sup>57</sup> For example, they note that “proper patient selection is critical,” requiring “a comprehensive benefit-to-harm evaluation that weighs the

---

the patients actually took, but also the possibility that other causes of death may have mistakenly been assessed as opioid-related. Furthermore, the Dunn study described only 6 deaths in its discussion of 51 overdose-related outcomes, and it did not differentiate between deaths and other overdose outcomes in its analysis. Thus, it is less informative on the question of an association between opioid dose and death.

<sup>56</sup> See Chou R, Fanciullo GJ, Fine PG, *et al.*, American Pain Society- American Academy of Pain Medicine Opioids Guidelines Panel. Clinical guidelines for the use of chronic opioid therapy in chronic non-cancer pain. *J Pain*, 2009; 10:113-130.

<sup>57</sup> See generally *id.*

potential positive effects of opioids on pain and function against potential risks.”<sup>58</sup> The guidelines also strongly recommend that “[o]pioid selection, initial dosing, and titration . . . be individualized according to the patient’s health status, previous exposure to opioids, attainment of therapeutic goals, and predicted or observed harms.”<sup>59</sup> The decision whether to proceed with opioid therapy, according to the guidelines, “should be intentional and based on careful consideration of outcomes” of the initial course of opioid treatment, which should be treated as a “short-term, therapeutic trial lasting from several weeks to several months.”<sup>60</sup>

These guidelines are consistent with the new indication for ER/LA opioids: a focus on treatment decisions that include a thorough patient-specific assessment of the appropriateness of ER/LA opioids for that patient, and that reflect careful thought by prescribers and patients alike.

## 2. *Cited Data on Persistence of Chronic Pain and Long-Term Opioid Use Are Inconclusive*

PROP cites surveys by Sullivan, *et al.*<sup>61</sup> and Eriksen, *et al.*<sup>62</sup> to support its assertion that “[r]ecent surveys of [chronic non-cancer pain] patients receiving [chronic opioid therapy] have shown that many continue to experience significant chronic pain and dysfunction” (Petition at 2). The Eriksen survey supports this assertion but is insufficient to conclude that chronic opioid therapy causes or contributes to chronic pain and dysfunction, or that it is ineffective in treating chronic pain and dysfunction. Although the survey found that the pain severity reported at the time of the survey was higher among respondents who were using opioids than those who were not using opioids, there was no assessment of pain severity prior to the time of the survey. Thus, patients who were using opioids could have suffered from higher levels of pain pre-survey than those who were not using opioids. Pain *improvement* was not measured.

The Sullivan survey found that patients with chronic non-cancer pain treated with chronic opioid therapy reported being in pain 162 of the past 180 days (90% of days), and 92% of that sample reported pain on at least 90 days. These data suggest that patients on chronic opioid therapy experienced significant chronic pain, and that they continued to experience pain throughout their therapy. However, the study did not survey similar patients who did *not* receive opioid treatment. Without such a comparison group, it is unclear what the patients’ pain trajectory would have been had they not been on chronic opioid therapy. Thus, this survey does not address the question of whether chronic non-cancer pain patients fare better or worse on chronic opioid therapy.

---

<sup>58</sup> *Id.* at 115.

<sup>59</sup> *Id.* at 117.

<sup>60</sup> *Id.*

<sup>61</sup> Sullivan MD, Von KM, Banta-Green C, Merrill JO, Saunders K. Problems and concerns of patients receiving chronic opioid therapy for chronic non-cancer pain. *Pain* 2010;149(2):345-353.

<sup>62</sup> Eriksen J, Sjogren P, Bruera E, Ekholm O, Rasmussen NK. Critical issues on opioids in chronic non-cancer pain: an epidemiological study. *Pain* 2006;125(1-2):172-179.

3. *Cited Data on Long-term Opioid Use and Addiction Do Not Establish a Threshold for Maximum Duration of Use*

PROP's Petition contends that opioids should be given a maximum duration of use based in part on a study of “[a] large sample of medical and pharmacy claims records[, which] found that two-thirds of patients who took opioids on a daily basis for 90 days were still taking opioids five years later” (Petition at 2).

FDA disagrees with this statement.<sup>63</sup> Although the study follow-up lasted roughly 5 years, not all patients who were started on chronic opioid therapy were followed for that duration. Approximately half of the study population was followed two years or less (the median follow-up time was around 2 years). Throughout the course of the study period, some patients were censored due to death, disenrollment from health coverage, or other reasons. Patients who were censored may have had a different duration of therapy than those who continued to be followed. In FDA’s view, the study showed that, among patients who were followed for 4.8 years, two-thirds were still taking opioids at the end of this period.

FDA also does not agree that these data necessarily reflect a safety concern specific to longer term use. Although some portion of these results certainly could be explained by adverse outcomes (e.g., addiction in opioid therapy patients), other factors may also be associated with low discontinuation rates (e.g., certain intractable or recalcitrant pain conditions that may require longer treatment periods). The referenced study did not collect data on why patients continued or discontinued opioid therapy, and without this information, it would be premature to restrict opioid use to a 90-day maximum duration treatment period.

The Petition also asserts that “[r]ecent surveys using [Diagnostic and Statistical Manual of Mental Disorders] DSM criteria found high rates of addiction in [chronic non-cancer pain] patients receiving [chronic opioid therapy]” (Petition at 2). FDA agrees with this assertion.<sup>64</sup> However, the cited surveys did not suggest that chronic opioid therapy causes addiction, or vice versa. Both addiction and chronic opioid therapy were measured at one point in time, so it is unknown which happened first: addiction or chronic opioid therapy.

The cited literature does not identify a duration threshold beyond which the risk of addiction outweighs the benefits of opioid treatment. PROP has selected a 90-day limit, but provides no evidence that addiction (however it is defined) increases significantly after 90 days of use such that it would support a labeling change. Nevertheless, the high

---

<sup>63</sup> See Martin BC, Fan MY, Edlund MJ, DeVries A, Braden JB, Sullivan MD. Long-term chronic opioid therapy discontinuation rates from the TROUP study. J Gen Intern Med 2011;26(12):1450-1457.

<sup>64</sup> However, the recently published Diagnostic and Statistical Manual of Mental Disorders – V (DSM V) combines the substance abuse and substance dependence categories into a single disorder measured on a continuum, to try to avoid an inappropriate linking of “addiction” with “physical dependence,” which are distinct issues. See American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fifth Edition. Washington, DC: American Psychiatric Association, 2013.

rates of addiction shown in the cited literature are concerning enough to require further exploration in postapproval studies.

#### 4. *Cited Data Are Insufficient to Explain Association between Opioid Use and Mental Health Co-Morbidities*

The Petition asserts that “[p]atients with mental health and substance abuse co-morbidities are more likely to receive [chronic opioid therapy] than patients who lack these risk factors, a phenomenon referred to as adverse selection.” In support of this assertion, PROP cites to a study by Edlund *et al.*,<sup>65</sup> which examined trends in opioid prescribing among individuals with non-cancer pain, with and without mental health and substances disorders.

Although the Edlund study supports the association between current mental health and substance abuse co-morbidities and current use of chronic opioid therapy, FDA is unable to determine the reasons for this association in a cross-sectional analysis. This study only depicts the frequencies and prevalence of chronic opioid therapy in different sub-populations at one point in time, and the temporal relationship between mental health and substance abuse comorbidities and opioid therapy cannot be established. Thus, it is difficult to form any conclusions based on this study regarding the relationship between mental health/substance abuse disorders and the initiation, dose and duration of chronic opioid therapy. In sum, FDA agrees with the study’s authors that the cited study does not conclude that the association between opioid use and mental/substance use disorder is due to any one specific factor.<sup>66</sup>

FDA acknowledges that patients with these co-morbid conditions may be at higher risk of adverse outcomes—possibly because they may be more likely to be treated with other psychoactive drugs. The results of the Edlund study thus underscore the need for prescribers to evaluate carefully whether and under what circumstances to prescribe opioids (particularly in high doses) to patients with these co-morbidities.<sup>67</sup> However, the findings of the Edlund study do not support PROP’s argument that opioid labeling should include a maximum daily dose or a maximum duration of use.

---

<sup>65</sup> Edlund MJ, Fan MY, DeVries A, Braden JB, Martin BC, Sullivan MD. Trends in use of opioids for chronic non-cancer pain among individuals with mental health and substance use disorders: the TROUP Study. Clin J Pain 2010;26:1-8.

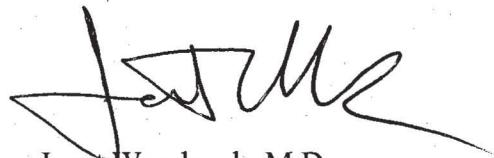
<sup>66</sup> The authors state that they “cannot definitively state why NCPC enrollees with MH [mental health]/SUDs [substances use disorders] were more likely to receive opioids than NCPC [non-cancer pain conditions] enrollees without MH/SUDs, and to receive them chronically[...].” *Id.* at 6.

<sup>67</sup> For example, section 5.1 of ER/LA opioid analgesic labeling, as provided for in the safety labeling change notification letters referred to above, contains the following language: “Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol addiction or abuse) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the prescribing of [Tradename] for the proper management of pain in any given patient. Patients at increased risk may be prescribed modified-release opioid formulations such as [Tradename], but use in such patients necessitates intensive counseling about the risks and proper use of [Tradename] along with intensive monitoring for signs of addiction, abuse, and misuse.”

**V. CONCLUSION**

For the reasons stated above, the Petition is granted in part and denied in part.

Sincerely,



Janet Woodcock, M.D.  
Director  
Center for Drug Evaluation and Research